the one of present application having SEQ ID NO:1 (D7: page 9, SEQ ID NO:3/4; D8: page 726, siRNA-F2). In this respect, It should be remarked that an oligonucletide which differs from one already characterized by being few bases longer or shorter, or by being shifted in the region of recognition by few bases, is considered as not involving an inventive step (Article 33(3) PCT) because such an oligonucleotide is merely one of several straightforward possibilities from which the skilled person would select, once identified a candidate region suitable for iRNA targeting and in accordance with circumstances, without the exercise of inventive skill, in order to solve the problem posed.

V.6). The subject-matter of claims 13, 26 and 39 differs from the disclosure of D5 in that certain p53 mutations are concerned.

The problem to be solved may therefore be regarded as the provision of further p53 mutants sensitive to c-FLIP inhibition.

The solution to this problem, as claimed in present claims **13, 26** and **39** cannot be considered as involving an inventive step for the following reasons: the position 248 concerned in part in claims 13, 26 and 39 is the same mutated in the HSC-4 cells disclosed in D5 (p53 mutation Arg248Glu, D6: pages 660-661). In this respect, it is not evident which contribution the specific mutations concerned in claims 13, 26 and 39 might provide to the method concerned in these claims, in terms of surprising or unexpected effects. As such, therefore, the specific mutations concerned in claims 13, 26 and 39 should be considered equivalent in their scope to the other p53 mutations for which an effect of c-FLIP inhibition was already characterized (see D5, already disclosed, and D1, commented below). They therefore represent merely some of several straightforward possibilities from which the skilled person would

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select, in accordance with circumstances, without the exercise of inventive skill, in order to solve the stated problem.

V.7). The subject-matter of claims **8, 9, 13-15, 21, 22, 26-28, 34, 35, 39-41, 43** and **44** (for claims 15, 28, 41, 43 and 44, insofar as an RNAi agent having nucleotide sequence as from SEQ ID NO:1 is concerned) does therefore not involve an inventive step (Article 33(3) PCT).

V.8). Document D10 describes a method of killing cancer HeLa cells comprising administration to said cells of (a) a c-FLIP antisense oligonucleotide and (b) cisplatin or Fas antibodies (D10: figures 6, 7 and relevant passages related thereto). HeLa cells contain no detectable p53 protein, due to HPV-mediated degradation of p53 itself (see D11: relevant passages throughout the entire article). Application of the results disclosed in this article for cancer therapy are also disclosed in D10.

The subject-matter of claims 3, 4 differs in part from the disclosure of D10 in that the cells concerned in the method claimed in claim 3 have a p53 mutation.

The problem to be solved may therefore be regarded as the provision of a further cells sensitive to c-FLIP inhibition.

The solution to this problem, as claimed in present claims 3 cannot be considered as involving an inventive step for the following reasons: a cell line which produces no detectable p53 (as the Hela cells) can be considered equivalent in its scope to a cell expressing mutant, inactive p53 and they can be interchanged where circumstances make it desirable. It would therefore be obvious to the person skilled in the art to conclude that the same effects noticed on Hela cells may also apply on other cells

bearing an inactive p53.

The subject-matter of claims **3, 4**, and consequently also of claims **17** and **30** does therefore not involve an inventive step (Article 33(3) PCT).

V.9). Document D1 describes a method of killing DU145 prostate cancer cells, comprising administration of a c-FLIP antisense oligonucleotide and of an agonist Fas antibody CH-11 (see relevant passages throughout the entire article, in particular, see figure 5 and passages related thereto). DU145 cells harbour a mutation in the p53 gene (see D4: relevant passages throughout the entire article).

The subject-matter of claim 5 differs from the disclosure of D1 in that a chemotherapeutic agent, chosen among a thymidylate synthase inhibitor, a platinum cytotoxic agent, or a topoisomerase inhibitor) is additionally administered.

The problem to be solved by present invention may therefore be regarded as the provision of a further method of killing cancer cells.

The solution to this problem, as claimed in present claims 5-12, 18-25, 31-38 cannot be considered as involving an inventive step for the following reasons: document D2 shows that treatment of DU145 cells with subtoxic concentrations of CDDP (a platinum cytotoxic agent), Adriamycin and Etoposide (both topoisomerase inhibitors, see document D3: abstract) followed by anti-Fas CH-11 treatment resulted in synergistic cytotoxicity and apoptosis (D2: relevant passages throughout the entire article).

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With reference to the part of claims 5-11, 18-24, 31-37 relating to coadministration of a thymidylate synthase inhibitor, document D5 shows that 5-FU may enhance susceptibility to FAS-mediated apoptosis (by the agonist antibody CH11) through downregulation of c-FLIP, and that antisense oligonucleotide to c-FLIP induces sensitization to Fas-mediated apoptosis in oral squamous cell carcinoma (OSCC) (D5: see relevant passages throughout the entire article).

Having regard to these disclosures, it would therefore be considered a normal option for the person skilled in the art to test the effect of CH-11 and CDDP, Adriamycin or Etoposide, or 5-FU, also in the presence of an antisense oligonucleotide against c-FLIP, as disclosed in D1. By doing so, the person skilled in the art would have arrived at a result falling within the scope of present claims 5-11, 18-24, 31-37 without intervention of any inventive skill and with a reasonable expectation of success, requiring nothing extraordinary, all being a matter of technical convenience.

Concerning the subject-matter of claims 8, 9, 21, 22, 34, 35 it should be remarked that the compounds oxaliplatin and CPT-11 can be considered equivalent in their scope to the compound CDDP, and can be interchanged with this latter compound where circumstances make it desirable. They therefore represent merely some of several straightforward possibilities from which the skilled person would select, in accordance with circumstances, without the exercise of inventive skill, in order to solve the problem of finding alternative platinum cytotoxic agents.

Concerning the subject-matter of claims 14, 27, 40, it should be remarked that small interfering RNA oligoribonucleotides can be considered equivalent in their scope to antisense oligonucleotides, and can be interchanged with these latter where circumstances make it desirable (see for example document D6). They therefore

represent merely some of several straightforward possibilities from which the skilled person would select, in accordance with circumstances, without the exercise of inventive skill, in order to solve the problem of finding alternative c-FLIP inhibitors.

The subject-matter of claims **5-11, 14, 18-24, 27, 31-37, 40** does therefore not involve an inventive step (Article 33(3) PCT).

V.10). The subject-matter of claims **1, 2, 16, 29,** the part of claim 42 related to a kit comprising a thymidylate synthase inhibitor or a topoisomerase inhibitor, and the parts of claims **15, 28, 41, 43, 44,** insofar as an RNAi agent having nucleotide sequence as from SEQ ID NO:2 is concerned, are considered as meeting the requirements of Article 33(3) PCT because, no document in the prior art would suggest, taken alone or even in combination with any other document, that a c-FLIP inhibitor might be used in cancer treatment as the sole cytotoxic agent, or to a combination of compounds comprising a c-FLIP inhibitor and a thymidylate synthase inhibitor or a topoisomerase inhibitor. Therefore, the person skilled in the art should have made use of inventive skills in order to derive the methods, uses, compositions and kit claimed in claims 1, 2, 16, 29 and 42. Analogously, the person skilled in the art should have made use of inventive skills in order to derive the specific RNAi agent as from SEQ ID NO:2.

V.11). The industrial applicability of the subject-matter of claims **16-44** is acknowledged (Article 33(4) PCT).

V.12). For the assessment of the present claims **1-15** on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for

example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Re Item VIII

Certain observations on the international application

VIII.1). Document D12 shows that treatment of chronic lymphocytic leukemia cells with c-FLIP antisense oligonucleotide was insufficient for triggering apoptosis (D12: figure 8 and passages related thereto).

Document D13 shows that treatment of IMR-32 neuroblastoma cells with c-FLIP antisense oligonucleotide was insufficient for triggering cell death (D13: figure 5 I, and passages related thereto).

Therefore, it should be concluded that c-FLIP inhibition is not applicable on all cancer cells, and that, consequently, the subject-matter of claims **1, 2, 16** and **29** is not sufficiently disclosed and supported over its whole breadth (Articles 5 and 6 PCT), indeed, it would be an undue burden for the person skilled in the art to discriminate between cells which might be suitable for such a treatment, and cells which would be insensitive to c-FLIP inhibition.

VIII.2). Present claims **1-13, 16-26, 29-39** relate to methods, uses and compositions

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involving or comprising a compound defined only in terms of a given desired property or effect, namely that it acts as a c-FLIP inhibitor. The claims cover all possible inhibitors whilst present application provides disclosure and support (Articles 5 and 6 PCT) only for a limited number of such inhibitors, *i.e.* antisense and RNAi molecules (see for example page 12 of present application). Therefore claims 1-13, 16-26 and 29-39 do not meet the requirements of Articles 5 and 6 PCT because their subject-matter is not sufficiently disclosed and supported.

Independent of the above reasoning, the claims also lack clarity (Article 6 PCT) because an attempt is made to define a subject-matter only in terms of a result to be achieved.